REMARKS

Status of the claims

Claims 1-6, 8-19, 25-27, 30, 34-40, 43, 46-48 and 51-56 are pending and under consideration. With this amendment, all pending claims are being cancelled without prejudice against their reintroduction into this or one or more timely filed continuation, divisional or continuation-in-part applications, and claims 57 – 68 are being newly added. Thus, after entry of this amendment, claims 57 – 68 are pending and under consideration.

Consonance with prior restriction and species elections

New claim 57 is the sole independent claim now presented for examination. Claim 57 is drawn to a method of treating idiopathic Parkinson's disease by administering safinamide, or a pharmaceutically acceptable safinamide salt, on a oral daily dosage schedule of about 0.5 mg/kg/day to about 2 mg/kg/day, and concurrently administering to the patient at least one Parkinson's disease agent, wherein the at least one Parkinson's disease agent is selected from L-dopa and dopamine agonists, and wherein the at least one Parkinson's disease agent is administered in an amount that alone has therapeutic effect. From a clinical perspective, claim 57 is drawn to use of safinamide as an add-on to ongoing treatment of idiopathic Parkinson's disease with L-Dopa or a dopamine agonist.

Claim 57 is consonant with applicants' prior election[1] of restriction Group I, "drawn to a method of treating Parkinson's Disease, comprising administering to a patient in need thereof a first composition comprising safinamide, a safinamide derivative or a MAO-B inhibitor and a second composition comprising at least one Parkinson's Disease agent, in an amount effective to treat said Parkinson's Disease in said patient."[2]

With respect to the species elections, claim 57 (*i*) reads specifically on the species previously elected for the first of the two concurrently administered compositions, safinamide or

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[1] Response to restriction requirement filed November 14, 2008.

[2] Restriction requirement mailed October 15, 2008, p. 2.

pharmaceutically acceptable salt thereof, and (*ii*) reads on, and is generic to, concurrent administration of L-Dopa, the species previously elected for the second of the two concurrently administered compositions.

Claims 58 – 67 depend directly or indirectly from claim 57, and read specifically on both of the previously elected species: concurrent administration of (*i*) safinamide or pharmaceutically acceptable safinamide salt, and (*ii*) L-dopa.[3]

Claim 68 depends directly from claim 57, and is drawn to concurrent administration of safinamide, or pharmaceutically acceptable safinamide salt, and a dopamine agonist. Claim 68 thus reads specifically on administration of safinamide as the species previously elected for the first composition, but does not read on applicants' election of L-Dopa as the species of the second composition. Claim 68 is marked as "new-withdrawn". Upon allowance of claim 57, which is generic to claim 68, applicants will be entitled to rejoinder and examination on the merits of dependent claim 68 and any claims hereafter added by amendment that depend directly or indirectly therefrom. 37 C.F.R. §§ 1.146 and 1.141(a).

Support for claims newly added by amendment

Support for the new claims is found throughout the specification, and particularly as follows:

Support for independent claim 57 can be found in the applicants' specification as a whole and particularly in the EXAMPLES, page 30, line 6, and lines 11 – 26.

Specific support for claim 58, drawn to addition of safinamide to therapy with L-Dopa, optionally with a peripheral decarboxylase inhibitor, is found in the specification particularly on page 18, lines 15 – 17.

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[3] Claim 67 reads on L-Dopa as the second elected species, notwithstanding the *further* addition of a dopamine agonist to the pharmaceutical regimen.

Specific support for claim 59, drawn to a daily dosage schedule of no more than about 2.0 mg/kg/day, is found in the specification particularly on page 19, lines 6 – 9.

Specific support for claim 60, drawn to daily dosage schedule of no more than 150 mg/day, is found in the specification particularly on page 19, lines 4 – 6.

Specific support for claim 61, drawn to administration for 12 weeks, is found in the specification particularly on page 30, line 9 and line 27.

Specific support for claim 62, drawn to administration once a day, is found in the specification particularly on page 30, line 27.

Specific support for claim 63, drawn to administration of the methanesulfonate salt of safinamide, is found in the specification particularly on page 10, line 28.

Specific support for claim 64, drawn to peripheral decarboxylase inhibitor selected from carbidopa and benserazide, is found in the specification particularly on page 4, lines 23 – 26.

Specific support for claim 65, drawn to catechol-O-methyltransferase inhibitor, is found in the specification particularly on page 18, lines 17 – 19.

Specific support for claim 66, drawn to tolcapone or entacapone, is found in the specification particularly on page 4, line 30.

Specific support for claim 67, drawn to a concurrently administered dopamine agonist, is found in the specification particularly on page 18, lines 19 – 21.

Specific support for claim 68, drawn to a concurrently administered dopamine agonist, is found in the specification particularly on page 4, lines 19 – 22.

Information Disclosure Statements

Applicants file concurrently herewith several distinct IDS statements, each listing distinct categories of references:

IDS 1

- all references not previously made of record that are cited in the specification of the instant application

IDS 2

- ISR and IPER for the international application of which the instant application is a §371 national phase, PCT/IB2004/001408
- references cited in the ISR
- Communications, Responses and Minutes of Oral Proceedings, European regional phase counterpart of the instant application, EP 040726590
- references cited in the Minutes of Oral Proceedings dated January 25, 2008, European regional phase counterpart of the instant application, EP 040726590

IDS 3

- exhibits 1 – 76 cited in the Declaration of C. Warren Olanow, filed concurrently herewith under 37 C.F.R. § 1.132

IDS 4

- U.S. Pat. No. 5,502,079, to Dostert *et al.*
- Press release, "Newron releases positive preliminary phase II data for safinamide in Parkinson's disease," Newron Pharmaceuticals S.p.A., dated January 9, 2003
- Chazot, "Safinamide – Newron Pharmaceuticals", *Curr. Opin. Investigational Drugs* 2(6):809-813 (2001)
- Maj *et al.*, "PNU-151774E, a combined MAO-B and glutamate release inhibitor, is effective in animal models of Parkinson's disease," Society for Neuroscience Abstracts 25 (1-2): p 1599 (1999) (Fariello, senior author)

Objections to the claims

Objection to claim 17 due to misspelling of "amantadine" has been obviated by cancellation of claim 17.

Rejections under 35 U.S.C. § 112, ¶ 1

Claims 1, 2, 8-10, 13-19, and 27 – now cancelled – were rejected under 35 U.S.C. §112, first paragraph, because the specification, acknowledged to enable use of safinamide as the species of MAO-B inhibitor, is said by the Examiner not to enable the treatment of Parkinson's disease with other MAO-B inhibitors, as had been more broadly claimed. Solely to expedite prosecution, and without acquiescence, applicants have obviated the rejection by amendment: all pending claims are now drawn in relevant part to administration of safinamide or pharmaceutically acceptable salts thereof. The rejection should be withdrawn.

Claims 1, 2, 8-10, 13-19, and 27, now cancelled, were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The rejection has been obviated by cancellation of all rejected claims, and would be in error if reasserted against the claims newly added by amendment herein, which are no longer drawn to adjunctive use of safinamide "derivatives" with "any Parkinson's disease agents." Accordingly, the rejection should be withdrawn.

Rejection under 35 U.S.C. § 112, ¶ 2

Claims 13 and 14, now cancelled, have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for (*i*) recitation of "levodopa/PDI" and (*ii*) the use of trademark/trade names. The rejection has been obviated by amendment: the language rejected by the Examiner has not been reiterated in the claims newly added by amendment herein. The rejection should be withdrawn.

Rejection Under 35 U.S.C. § 102(b)

Claims 1, 2, 18 and 19 were rejected under 35 U.S.C. §102(b) as being anticipated by Fredriksson *et al.*, "Effects of co-administration of anticonvulsant and putative anticonvulsive agents and sub-/suprathreshold doses of L-Dopa upon motor behaviour of MPTP-treated mice," *J. Neural. Transm. 106:889-909* (1999) ("Fredriksson"). The rejection has been obviated by

cancellation of the rejected claims. The rejection would be in error if renewed against the claims newly added by amendment herein, which include at least the following elements not disclosed in Fredriksson:[4] (*i*) treatment of *human* patients with *idiopathic* Parkinson's disease[5], in contrast to Fredriksson's experiments on mice acutely lesioned with MPTP; (*ii*) oral administration of safinamide, as contrasted to subcutaneous dosage in Fredriksson; (*iii*) daily schedule for dosing safinamide, as contrasted to Fredriksson's single administration of safinamide; and (*iv*) concurrent administration of the Parkinson's disease agent in an amount that alone has therapeutic effect. Lacking elements of applicants' claims, Fredriksson cannot anticipate and the rejection should be withdrawn.

Rejection Under 35 U.S.C. § 103(a)

Claims 8, 9, 10, 13, 14 and17 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Fredriksson as applied under § 102(b) to claims 1, 2, 18, 19 above in view of Edgren (U.S. Pat. No. 6,217,905). Claims 15 and 16 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Fredriksson as applied to claims 1, 2, 18, 19 in view of Chenard (U.S. Pat. No. 6,258,827).

The rejections have been obviated by cancellation of the rejected claims.

Furthermore, any rejection under 35 U.S.C. §103 of new claims 57 – 68 over Fredriksson – taken alone or in combination with any reference now of record – would be in error for the reasons advanced in the Declaration of C. Warren Olanow, filed concurrently herewith under 37 C.F.R. § 1.132.

Applicants will not here reiterate the entirety of Dr. Olanow's declaration, and instead summarize Dr. Olanow's conclusions, and certain of Dr. Olanow's comments, and commend the Examiner's attention to the supporting details set forth in the Declaration and exhibits referenced therein.

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[4] Fredriksson's experimental protocols are described in detail in the accompanying Declaration of Dr. C. Warren Olanow, and thus will not be repeated in detail here.

[5] Idiopathic Parkinson's disease is by definition a disease uniquely seen in human beings.

Dr. Olanow is among the world's leading experts in translating the preclinical science of Parkinson's disease into approved medical treatments. *See* Olanow Declaration, ¶¶ 1 – 11. In the period 1996 – 2006, which spans the instant application's priority and international filing dates, Dr. Olanow was ranked #1 in the United States and #4 in the world for the number of citations in Parkinson's Disease. Olanow Dec., ¶ 11. His *Curriculum Vitae* is enclosed as Exhibit 69 to his Declaration.

In light of the invention as now claimed,[6] Dr. Olanow was asked to consider two questions:

> (*i*) Would the disclosure in the Fredriksson reference have provided a person of ordinary skill in the art of Parkinson's disease therapy, in April 2003, with a reasonable expectation that the oral administration of safinamide (or safinamide salt), on a daily dosage schedule of about 0.5 to about 2 mg/kg/day (or on a daily dosage schedule of no more than about 150 mg/day), would increase the therapeutic efficacy of a clinically effective dose of concurrently administered L-Dopa, administered with a peripheral decarboxylase inhibitor, in the treatment of idiopathic Parkinson's disease?
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> (*ii*) Would the additional disclosures in the Chazot[7] and Fariello[8] references change that assessment?

Olanow Dec., ¶ 16. For the reasons elaborated at length in his Declaration, and briefly outlined below, Dr. Olanow "would answer both questions in the negative," *Id.*

Fredriksson used MPTP-lesioned mice to model Parkinson's disease, and to test various agents, including safinamide (aka FCE 26743), for their potential when used alone and in various combinations to improve the animals' experimentally-induced motor symptoms. The MPTP model is well known, and widely used in preclinical research. Olanow Dec. ¶¶ 18, 19. Despite its wide use, however, the MPTP model is well known in the art to suffer from limitations that

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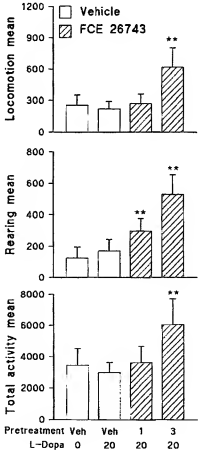
[6] Reading claim 57 in light of applicants' election of L-Dopa as the species of concurrent therapy onto which safinamide is to be adjunctively added.

[7] Chazot, "Safinamide – Newron Pharmaceuticals", *Curr. Opin. Investigational Drugs* 2(6):809-813 (2001).

[8] Maj *et al.*, "PNU-151774E [aka, safinamide], a combined MAO-B and glutamate release inhibitor, is effective in animal models of Parkinson's disease," *Society for Neuroscience Abstracts* 25 (1-2): p 1599 (1999) (Fariello, senior author).

generally reduce its ability to predict an agent's efficacy in treating idiopathic Parkinson's disease in human beings. Olanow Dec. ¶¶ 21 – 24. And as particularly adapted and used by Fredriksson, "there are several specific aspects of the reported experiments that particularly reduce the predictive value of these experiments, and thus warrant particular mention." Olanow Dec., ¶ 25. In particular,

> [a]lthough Fredriksson labels the 20 mg/kg dose of L-Dopa in the "chronic" experiment as a "suprathreshold" dose, the terminology is misleading: as with the "subthreshold" 5 mg/kg dose in the "acute" experiment, the 20 mg/kg L-Dopa dose in the "chronic" experiment **is itself ineffective and does not reverse MPTP-caused motor deficits**; accordingly, the L-Dopa dose in the "chronic" experiment should more properly have been labeled as a "subclinical" dose. This can best be seen by comparing the two left-most bars in each histogram of Fredriksson's FIG. 6, reproduced below: in the absence of pretreatment with safinamide, the administration of 20 mg/kg L-Dopa has no significant effect on any of the measured activities:



> At the time, safinamide was already known to have potent and selective MAO-B inhibitory activity,[9] and would on that basis reasonably have been predicted to be effective as monotherapy in the treatment of Parkinson's disease (see my own reports on selegiline and lazabemide, *e.g.*, Parkinson's Study Group, Olanow CW, Steering Committee, "Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease," *N. Eng. J. Med.* 328:176-183 (1993) (Exhibit 75)). All Fredriksson adds to the then-existing body of knowledge is evidence that pretreatment with a single dose of safinamide can improve the efficacy of L-Dopa at doses of L-Dopa that, by themselves, are ineffective in what he terms the "acute" and "chronic" MPTP models. This result is not inconsistent with safinamide's known MAO-B inhibitory activity.
>
> Limited to experimental conditions in which L-Dopa was administered at doses that by themselves were clinically ineffective, **the Fredriksson experiments simply do not model or mimic any phenomenon that is relevant to treatment of Parkinson's patients**: physicians would never administer subtherapeutic doses of L-Dopa. Indeed, subtherapeutic doses of levodopa might worsen the parkinsonian status of a PD patient by acting on presynaptic dopamine receptors and thereby inhibiting dopamine synthesis and release. **The Fredriksson data simply do not speak to the relevant question, whether concurrent administration of safinamide would increase the therapeutic efficacy of therapeutically-effective doses of L-Dopa**.

Olanow Dec., ¶¶ 29 – 31 (emphasis in the original).

Furthermore, Fredriksson administered safinamide parenterally, by subcutaneous injection.

> Safinamide is being developed as an oral, not subcutaneous, treatment for Parkinson's disease. This is an important distinction. Effects seen with parenteral administration often will not reliably predict effects obtained oral administration, and vice versa. The reason is that drugs administered orally are subject to first-pass metabolism in the liver, whereas drugs administered parenterally are not. Orally administered agents can thus have a very different pharmacologic profile (and are often effectively different drugs) than when the same agent is administered via the subcutaneous route.

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[9] Strolin-Benedetti *et al.*, "The anticonvulsant FCE 26743 is a selective and short-acting MAO-B inhibitor devoid of inducing properties towards cytochrome P450-dependent testosterone hydroxylation in mice and rats," *J. Pharm. Pharmacol.*46:814-819 (1994) (Exhibit 74); U.S. Pat. No. 5,502,079 (of record) [footnote 6 in Olanow Declaration].

Olanow Dec., ¶ 32; see also ¶¶ 33 – 35. For these and other reasons further detailed in his Declaration, Dr. Olanow concludes that

> the animal model data in the Fredriksson reference would not have provided a person of ordinary skill in the art, in April 2003, with a reasonable expectation that the oral administration of safinamide would increase the therapeutic efficacy of ***clinically-relevant*** (that is, therapeutically effective) doses of L-Dopa being concurrently administered to patients with idiopathic Parkinson's disease.

Olanow Dec., ¶ 37 (emphasis in the original).

It is black letter law that a ***prima facie*** case of obviousness requires a reasonable expectation of success. *See, e.g.*, M.P.E.P. § 2143.02 (8th ed., rev. 6). Because there would have been no such reasonable expectation that the oral administration of safinamide would increase the therapeutic efficacy of clinically relevant (that is, therapeutically effective) doses of L-Dopa, it would be legally improper to bring such rejection of applicants' now-pending claims.

Conclusion and interview request

Claims 57 – 68 are believed to satisfy all of the criteria for patentability and are in condition for allowance. An early indication of the same is therefore respectfully requested. If the Examiner believes that any matters remain outstanding before passing the claims to issue, applicants request that the Examiner call the undersigned attorney of record to schedule a personal interview before issuance of a subsequent action.

The Director is authorized to charge any additional fees that may required, or credit any overpayment, to Dechert LLP Deposit Account No. 50-2778 **(Order No. 373897-011US (102895)**.

Respectfully submitted,

Date: JUNE 24, 2009

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